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Iron Nutrition

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IN VIEW OF the abundance of iron on this planet, it is not surprising that this metal would be chosen for the critical function of oxygen transport. Elaborate systems regulating iron exchange with the environment and the transport of iron within the body have evolved. While these appear quite adequate for most animal species, there is reason to question their effectiveness in man. World-wide, iron lack is the commonest deficiency state encountered. In large segments of the population both the amount and availability of ingested iron is insufficient to replace the small quantities of iron normally lost. This review will attempt to clarify the nature of external iron exchange between man and his environment. Attention will be focused on the population at large rather than on pathologic mechanisms affecting iron metabolism.

Iron Balance in Humans

Functional or essential body iron contained in circulating hemoglobin, myoglobin and intracellular iron-containing enzymes represents about 35 mg of iron per kg of body weight. Beyond this there is a variable quantity of storage iron which serves as a buffer against sudden losses due to bleeding or for the needs of pregnancy. In adult men storage iron represents about 15 mg per kg of body weight or one third of total body iron, whereas in women storage iron varies widely between 0 and 20 percent of total body iron.

Daily requirements for iron are dictated by a small and constant obligatory loss from the body. In a normal 70 kg (154 pound) man this averages about 10 percent of body iron per year or about 0.9 mg per day.[1] Two thirds of this loss occurs via the gastrointestinal tract of which roughly one half or 0.4 mg is due to extravasated red blood cells.[1] Additional small losses occur via the skin and urinary tract. While total losses vary somewhat in relation to the amount of body iron, the limits of such compensation are narrow, from perhaps 0.5 mg with severe iron deficiency to 2 mg with iron overload.[1-3]

In normal women substantial additional losses of iron occur as a result of menstruation. Studies in different geographic areas have yielded surprisingly similar values for menstrual loss which amount to about 40 ml of blood each month or a daily loss of 0.5 mg of iron.[4-6] The distribution of this menstrual loss within a population is highly skewed and 5 percent of women have losses of more than three times this amount.[4] Additional iron losses occur in women during pregnancy due to the needs of the growing fetus and placenta. The net cost of pregnancy is 500 to 700 mg of iron.[7-10] Growth in infancy through adolescence also imposes increased iron needs.

To balance these physiologic requirements a constant influx of iron from the diet is required.

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The amount of dietary iron is closely tied with caloric intake, and the iron to calorie ratio (6 mg per 1,000 kilocalories) varies remarkably little in different economic segments of the population.[11] In adult men with an average intake of about 2,500 kilocalories and an iron intake of 15 mg per day, only 6 percent of ingested iron need be absorbed to maintain iron balance. Stores of ferritin and hemosiderin in normal man average about 1,000 mg, sufficient iron to replace normal losses for three years if absorption were to be completely abolished. Therefore the appearance of iron deficiency in man almost always signifies an excessive iron loss, usually due to bleeding from the gastrointestinal tract. In addition, a man on a typical American diet can maintain body iron in the face of loss as high as 2.0 to 3.0 mg of iron or 16 to 20 percent of dietary intake.[10] Iron balance in menstruating women is much more precarious. Dietary iron intake amounts to about 11 mg per day so that with average requirements of about 1.3 mg per day, 12 percent of ingested iron must be absorbed to maintain balance. Average stores in menstruating women amount to about 300 mg or about one third of the level in men.[12-14] These stores are considerably less than the demands of a normal pregnancy, a fact that explains the very common occurrence of iron deficiency during pregnancy if additional iron is not given.[8,10,15-18] From these general studies of iron balance it is apparent that there is a limited capacity of absorption to meet increased requirements in those segments of the population with special needs. Some of the reasons for this have only recently been clarified through studies of iron absorption.

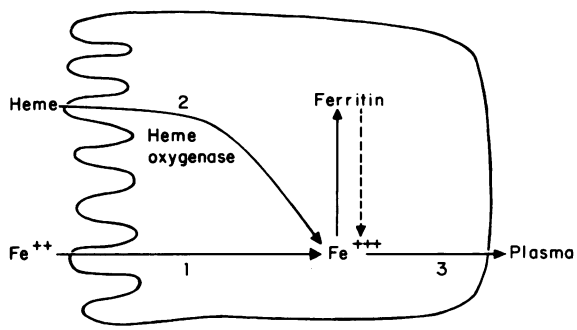

Figure 1.—Iron transport by the intestinal mucosal cell. There are two pathways by which iron from the lumen of the gastrointestinal tract can enter the mucosal cell. The major pathway is in the form of reduced ionic iron (1) which represents the largest portion of ingested dietary iron. Iron can also enter the mucosal cell as an intact porphyrin complex (2) which is degraded within the cell by heme oxygenase with release of iron to the intracellular pool. From the latter, iron is either transported to the serosal surface when it enters the circulation (3) or is incorporated into ferritin as storage iron (4). Although a portion of this storage iron may be available for later transport into the body (interrupted line) most of this iron is lost from the body when the mucosal cell is sloughed at the end of its 4 to 5 day life span.

The Absorptive Mechanism

The interface between ingested iron and body iron resides in the mucosal cell of the upper small intestine. By controlling entry of iron into the body, the intestinal mucosa determines the amount of total body iron. There are two chemical forms of iron which enter the mucosal cell from the intestinal lumen (Figure 1). One of these is ionic iron, assumed to be largely reduced iron due to its greater solubility.[19] This ionic iron is initially bound to the brush border before being transferred into the mucosal cell.[20] This portal of entry is not specific for iron but is apparently shared by and can be competitively inhibited by a variety of heavy metals including cobalt, manganese and zinc—but not copper or magnesium.[21-24] The other absorbable form of iron is as a porphyrin complex derived from hemoglobin and myoglobin.[25-28] Once within the mucosal cell, this heme iron is enzymatically degraded and the released iron enters the ionic pool of mucosal iron.[27,29,30]

Following entry into the mucosal cell there are two major pathways of iron transfer. A portion of newly absorbed iron is rapidly transported to the serosal side of the cell where it gains entry into circulation. This rapid phase of iron transport is undoubtedly mediated by a specific carrier protein[31-36] and recent studies have provided some evidence that this may be transferrin.[37] The alternate pathway for iron is its incorporation into ferritin. Despite much recent study of intracellular transport of iron by the mucosal cell, the biochemical events of this process are still poorly understood. Whereas earlier studies suggested that ferritin was intimately involved with iron transport by the mucosal cell into the body, iron enters this fraction only after the rapid phase of iron transport is largely completed. Incorporation of absorbed iron into ferritin, therefore, appears to be a passive phenomenon for the storage of iron which has not been transported out of the cell.[38] Although a portion of ferritin iron may later be transferred into the body, most iron in this form

is lost from the body with exfoliation of the mucosal cells.[39-42]

Mucosal Regulation

Regulation of iron absorption by the intestinal mucosa functions so as to maintain an adequate complement of body iron. Experimentally, a large number of factors have been shown to modify iron absorption, the most important of which include body iron stores,[43-46] the rate of erythropoiesis,[43,47-49] and hypoxia.[50-53] In human subjects without disorders in intestinal absorption or internal iron metabolism, the main determinant of iron absorption is the level of body iron stores.[3,54-56] Absorption is enhanced not only with frank iron deficiency anemia but also in latent iron deficiency where a reduction in iron stores has not yet affected the level of plasma iron. Thus, blood donors with no evidence of iron deficient erythropoiesis absorb iron at a level twice that of nondonors,[46] and women with their lesser iron stores absorb iron at a rate twice that of normal men.[57] During pregnancy a progressive rise in iron absorption is observed as iron stores become gradually depleted.[54] Conversely, enlargement of iron stores by parenteral iron administration results in decreased iron absorption.[44]

Despite an intensive search for a mechanism by which these alterations exert their influence on the mucosa, a specific humoral regulator which could account for all experimental observations has not yet been identified. A hypothesis to account for this reciprocality between iron stores and iron absorption was advanced by Crosby and coworkers.[39-42,58-61] It was proposed that iron supplied from the plasma to the mucosal cells during their formation in the crypts of Lieberkühn conditioned the cell for its subsequent handling of luminal iron. In persons with lower iron stores less iron would be supplied to the mucosal cell which would then transport increased amounts of luminal iron during the four to five day cell life span. A higher supply of body iron would have a reciprocal effect. Despite many attractive aspects of this hypothesis it does not explain the signal from iron stores to the mucosa which operates in persons with normal hemoglobin, normal plasma iron, normal transferrin saturation and normal plasma iron turnover.

Luminal Factors

For the intestinal mucosa to perform its function in regulating iron stores, there must be sufficient quantities of luminal iron in a form which can be assimilated. Factors within the gastrointestinal tract which influence the assimilation of nonheme iron are to some extent predictable on the basis of the physiochemical properties of the metal. The limitation of iron absorption to the upper part of the small intestine is undoubtedly explained by the increase in pH below this region of the gut which precipitates ferric iron as an insoluble macromolecular complex. Several studies have shown that persons with achlorhydria absorb iron less well, indicating some importance of gastric secretion.[62-66] It has also been suggested that another constituent of gastric juice facilitates absorption by forming small molecular complexes with iron which remains soluble at a pH above 5.[67] Conversely, a high molecular weight iron-binding substance in gastric juice, called gastroferrin, has been described and was believed to prevent iron absorption.[68-70] Later studies, however, have not confirmed the importance of gastroferrin as a regulator of iron absorption.[71,72] Experimentally, a reduction in pancreatic secretion has been shown in animals to enhance iron absorption[73-75] and in humans, chronic pancreatitis has been proposed as a cause of excessive accumulation of body iron.[76-80] Recent workers have doubted the importance of pancreatic secretion *in* disorders in iron balance.[81-83] In summary, despite a number of reports proposing otherwise, luminal factors other than pH have not been yet established as important in iron absorption. The only clinical abnormality in the luminal phase of iron absorption which frequently leads to iron deficiency is partial gastrectomy, where a disturbance in gastrointestinal motility even more than gastric secretion appears to be responsible.[84-88]

Dietary Factors

In human iron nutrition, the most important considerations are the amount of iron and type of diet in which it is ingested. While the amount of dietary iron has long been a matter of concern, its limited availability has been obscured by extrapolating data obtained in small laboratory animals to man. Rats for example have been used extensively in studies of human iron nutrition. However, the capability of rats for iron absorption is quite different from that of humans: nonheme iron is much better absorbed than in humans, but heme iron less well.[27]

In recent years, extensive isotopic measurements of food iron absorption have been made in

humans, which make extrapolation from animal studies unnecessary. The problem with isotopic measurements of food iron availability in humans has been the great variation in measurements.[46,89] A large portion of this variation is due to differences in absorption within the same person when tested on different days. This day-to-day variation can be reduced by partitioning the test dose over several days[90] and by including a sufficient number of subjects in each study to obtain statistically meaningful data. The remaining component of variability is due to differences between persons studied, which in turn reflect differences in their level of iron stores. This type of variation can be circumvented by doing multiple absorption studies in the same person using two radioiron tracers.[46,90] Since iron status varies appreciably in different geographic regions of the world, absorption tests should always include a standard reference dose of inorganic iron.[91] By expressing absorption of food iron relative to this reference dose rather than as an absolute measurement, studies performed in subject groups of widely different iron status can be compared.

Initial efforts to understand food iron absorption employed single food items which had been biosynthetically labeled as first described by Moore and Dubach.[92] This was accomplished by growing vegetal foods in hydroponic media tagged with radioiron and by injecting radioiron intravenously into animals several months before they are killed. Data obtained by these techniques have been reviewed.[93-95] The most important finding in such studies was the much lower availability of vegetal sources of iron as compared with animal tissues. For the former, mean absorption ranged from a low of 1 to 2 percent from rice and spinach to a high of 6 to 7 percent from soybeans. Absorption from maize, black beans and wheat—which are all staple food items in various areas of the world—had intermediate levels of absorption of 3 to 4 percent with a ceiling in iron deficient subjects of about 10 percent. Absorption from animal sources which have included beef, fish and liver were at substantially higher levels of 15 to 30 percent and approached the absorption rates of comparable doses of ferrous sulfate. The limitation of such single-item absorption studies became apparent when two foods were administered simultaneously, each of which has been biosynthetically tagged with separate isotopes of iron. For example, when fish is administered with maize, absorption of the former is decreased to about a half while the latter is nearly doubled.[96] In view of the complexities of a modern diet, studies with biosynthetically tagged foods have limited application to the evaluation of food iron nutrition. Unless a way was found to evaluate iron absorption from a complete meal, absorption data would have little meaning.

The measurement of food iron absorption has recently been shown to be possible in a different manner. The technique is based on the extrinsic radioactive tagging of dietary heme and nonheme iron. It was initially observed that when a small quantity of inorganic iron was mixed with a vegetal food at the time of administration, absorption of this extrinsic tag was nearly identical with that of the biosynthetic or intrinsic radioiron tag.[97] This observation has been validated now for a large number of vegetal foods and in several laboratories.[98-103] An important extension of these findings was the demonstration that if an homogenized meal containing several vegetal foods was tagged extrinsically, absorption of the extrinsic tag was nearly identical to any one of the food items which had been intrinsically labeled.[97] This provided convincing evidence that for foods ingested simultaneously, a common pool of absorbable nonheme iron is formed, the absorption of which could be measured with an extrinsic tag. The same principle could be employed to measure absorption of dietary heme iron by adding a small amount of radioactive hemoglobin to the meal.

By adding different radioisotopes of iron to separately label the heme and nonheme iron pools, total iron absorption from a complete meal could be determined.[103-107] The two pool extrinsic tag method has yielded measurements of food iron absorption which agree closely with estimates based on normal body iron loss. For example, meals composed of aliquots of all foods consumed in a typical six weeks' diet and doubly tagged with radioactive heme and nonheme iron were administered to 32 young men.[107] The total daily intake of iron in these men was 17.4 mg, of which only 1 mg was in the form of heme iron. Total absorption averaged 1.25 mg per day. Absorption of nonheme iron averaged 5.3 percent or 0.88 mg per day whereas absorption of heme iron averaged 37 percent or 0.37 mg of iron. Similar data have been obtained by Martinez-Torres and Layrisse[104] who employed a meal of meat, black beans, maize and rice containing a total of 4.5 mg of iron. In normal persons, absorption from 1.5 mg of heme iron was 27 percent or 0.34 mg as compared with

an absorption from 3.0 mg of nonheme iron of 6 percent or 0.12 mg. Total absorption from the meal was, therefore, 0.46 mg of iron. In iron deficient persons, absorption from heme and nonheme iron increased to 37 percent (0.52 mg) and 14 percent (0.43 mg) respectively to give a total iron absorption from the meal of 0.95 mg. These studies indicate that when meat is consumed regularly in the diet, relatively small amounts of heme iron may account for a sizable portion of food iron absorption. Unfortunately, the intake of heme iron in an appreciable portion of the world population is negligible.

Evidence that the absorption from the nonheme pool may be notably influenced by the composition of the diet has focused attention on those substances within the diet which affect availability. Ascorbic acid is a potent enhancer of iron absorption, not only because of its ability to reduce iron but also by forming a chelate with ferric iron at low pH which remains soluable at the higher pH of the duodenum. Recent studies have shown an enhancing effect on nonheme iron absorption of relatively small amounts of ascorbic acid either contained in or added to food during its preparation.[100,101,103,105] For example, 60 mg of ascorbic acid added to a meal of rice more than tripled absorption of iron[102] and 150 grams of papaya containing 66 mg of ascorbic acid increased iron absorption more than five fold when taken with a meal of maize.[105]

Animal tissues such as meat also greatly facilitate nonheme iron absorption. The substitution of 100 grams of beef for an equivalent amount of protein as egg albumin in a test meal increased absorption more than five times.[108] Meat is, therefore, doubly important: on the one hand as a source of heme iron and on the other because of its ability to enhance the absorption of nonheme iron. Inhibitors may be assumed to be present in large amounts in vegetal food because of the very low intrinsic availability of iron. Phosphates are known to impair iron absorption by the formation of insoluble complexes of iron within the duodenum. This is particularly true of phytate, illustrated by the pronounced inhibition of iron absorption by bran present in whole wheat bread.[109] Ethylenediamine tetraacetic acid (EDTA) is another blocking substance which, at levels employed as a food preservative in our diet, reduces iron absorption by effectively competing with the mucosal cell for iron.[108] As yet, studies of these dietary factors have not progressed sufficiently to define their relative importance in the American diet.

Perspectives

There can be no question of the widespread nature of iron deficiency. Anemia, which may have been an appropriate clinical measurement in past studies of nutritional anemia, is imprecise and often misleading as a screen for iron deficiency in the general population.[110,111] An extensive study by the World Health Organization indicated that iron deficient erythropoiesis, as identified by a transferrin saturation of less than 16 percent, occurs twice as frequently as iron deficiency anemia.[112] More recently, serum ferritin provides a means of evaluating tissue iron stores and defines a still larger group with iron depletion.[14,113] Such measurements leave no question but that a large portion, perhaps 20 percent of the world's 3.6 billion people, are iron depleted in the sense that adequate stores cannot be sustained despite near maximal absorption.

When women become overtly anemic due to iron lack, the cause is usually not an abnormality of mucosal cell function but rather ingestion of an insufficient quantity of available dietary iron or excessive losses of iron through bleeding or both. There has been a tendency to blame bleeding for most iron deficiency. Clearly bleeding in excess of 5 ml per day will exceed the limited capacity of dietary iron absorption. Clearly also, the most anemic persons in any population will be those who have bleeding superimposed on dietary limitations. While equating iron deficiency with blood loss is proper in men, this is not appropriate in vulnerable populations with increased iron requirements—for instance, infants, adolescents and menstruating and pregnant women. Current information indicates that the vast majority of the population with depleted iron stores appear to have only "physiologic" iron losses, adequately explained by an availability of about 5 percent of iron in meals not containing meat or significant amounts of ascorbic acid. The correlation between protein deficiency as measured by the serum albumin and iron deficiency lends support to the importance of meat in the diet.[113] Some compensation is achieved in some parts of the world by iron contamination of food resulting in an increased total iron intake of 150 to 200 percent that of native food.[114] Even so, dietary iron assimilation is borderline due to low availability. In developing countries availability appears to be

most critical whereas in developed countries the amount of iron ingested appears most limiting.

It is helpful to consider the adequacy of dietary iron in humans in relation to other species. All vertebrates have been faced with a hundredfold increase in iron requirements when heme became the vehicle for oxygen transport, yet iron deficiency is considered rare in most undomesticated species. Only in rats has iron balance been examined in detail and such studies show major differences from humans. The intake of dietary iron in rats is over 100 times that of humans when expressed per kilogram of body weight.[115] However, when these animals are placed on a restricted dietary iron supply, they can assimilate about 50 percent or more of nonheme iron of a type which would be of low availability (about 10 percent) in man.[116] Iron deficiency can be produced in rats only under the most stringent dietary restrictions and during periods of rapid growth.[117] Along with greater intake and more efficient absorption, these animals possess an effective system for excreting body iron through the gastrointestinal tract.[118] In man on his customary diet, the amount of iron which can be absorbed or excreted appears to be about 1 percent of that exchanged in rats, per kilogram of body weight.[115]

It seems reasonable to assume that man evolved his special ability to conserve iron, in response to a diet very low in iron and a low availability of dietary iron, through evolutionary changes which were valuable at the time they occurred. The similarity of iron exchange among Homo sapiens throughout the world indicates that this is a characteristic of man as a species and it must be presumed to have evolved long ago. The more difficult questions to answer are what constituted iron balance then and what changes have been imposed by civilization. Man's history as a highly skilled hunter with a strong dependence on animal food goes back at least a million years.[119] Meat is a portable concentrated food and in the paleolithic period it apparently was harvested from migrating herds and possibly stored by smoking or drying.[120] Fruit too, with its ascorbic acid content, may be presumed to have contributed significantly to dietary iron availability. In the comparatively recent history of man, profound changes in dietary habits seem to have occurred. The domestication of plants, occurring some 10,000 years ago, began the transition to predominately vegetable diets and the pressure of expanding human population made such low cost nutrients a necessity. It has been estimated that in less than 450 generations, the approximate contribution of animal foods in the diet has shrunk from about 70 to 5 percent.[119] Such changes would be anticipated to reduce the availability of dietary iron. Other more recent changes further reducing iron supply include a decreased physical activity and a parallel reduction in caloric and iron intake and the removal of contaminating iron from food. As a final insult, chelates have been added to prevent oxidation of preserved foods by metal ions and their presence acts to further reduce the availability of iron. Improved feeding has increased the size of infants, adolescents and adults with a parallel increase in iron requirement. It would seem that changes of civilization have confronted man with a dietary intake of iron inconsistent with his previously established genetic makeup. A similar line of reasoning may be applied to the iron deficiency observed in domesticated animals, such as pigs and wild animals held in captivity.

The solution to man's problem would appear simple; to provide additional iron to food and thereby realign dietary iron with man's needs. The acceptance of this philosophy is reflected in the fact that about 20 percent of iron intake in the United States and about 40 percent in Sweden is supplied by fortification of food. Such fortification has been carried out to date with no meaningful evaluation of its impact on iron balance. Indeed the effort may have been partially abortive since certain salts used for fortification have been shown to be of extremely low availability. Large particle ferrum reductum has been shown to be relatively unavailable;[121] sodium pyrophosphate is approximately 5 percent and ferric orthophosphate is about 30 percent available as reduced iron of small particle size or ferrous sulphate mixing completely with food iron.[122] Planning for fortification must then involve the use of available iron salts. To such planning must be added an appreciation of iron's availability in the diet eaten by a iron-depleted population. For example, Layrisse has shown that when as much as 60 mg of iron as ferric chloride is added to a meal not containing meat, this results in the absorption of only 0.3 mg of iron.[123] These considerations provide some initial guidelines to fortification. When the total iron content of the diet is low, supplemental iron of a high availability type may suffice; when iron content is more adequate but availability is very low, fortification of the diet with an enhancing substance such as ascorbic acid, rather than

adding additional iron, may be the more effective approach. While improving the iron nutrition of the population seems a worthy cause, its success will depend on further studies of food iron availability and on careful evaluation of the effectiveness of those dietary changes which are undertaken.

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